were then incubated with lysates from cells expressing Flag epitope-tagged Grb14 [Daly *et al.* 1996 *supra*) or human breast cancer cells expressing high levels of Grb7 (SK-BR-3: Stein et al. 1994) as described previously (Daly et al. 1996). Following washing, bound proteins were detected by Western blot analysis. The results indicated that 2.2412 bound specifically to both Grb14 and Grb7 *in vitro*, and that the N-terminal fusion protein bound more strongly than that derived rom the C-terminus. These data, obtained using a different methodology for detecting protein-protein interactions to the yeast two hybrid system. confirm that 2.2412 interacts with Grb14. Furthermore, 2.2412 also binds Grb7. Consequently 2.2412 appears to represent a general effector for the Grb7 family.

REMARKS

In an Office Action dated December 3, 2001, claims 1-7, all of the claims under consideration in the subject patent application, were rejected. By amendment above, claims 1, 5 and 6 have been rewritten to further define the invention. Support for the rewritten claims can be found on page 3, lines 10-13, page 5, lines 17-19, page 11, lines 10-11 and page 11 lines 29- 32 of the specification. Support for the new claim 19 can be found on page 3, lines 14-16 and support for new claims 20 and 21 can be found on page 3, lines 21-22.

Reconsideration of this application and allowance of the claims is respectfully requested in view of the foregoing amendments and the following remarks.

The Examiner asserts that the application should contain as the first line of the specification a statement that the application is the national stage entry of PCT/AU98/00795,

filed September 23, 1998 as a claim of priority. Applicants have amended the application accordingly, inserting into the application on the first line a statement that this application is a national stage 371 application of PCT/AU98/00795, filed September 23, 1998 from which priority is claimed.

The Examiner required correction of the drawings as indicated on the "Notice of Draftperson's Patent Drawing Review," PTO-948 attached to the Office Action. The Examiner states that the figures of the application are presented on seperate pages or in seperate panels and requires correction as required by 37 CFR 1.84(u)(1). Applicants submit herewith proposed corrected drawings to reflect the seperate numbering requirement and have amended the specification to correct the reference to the drawings reflecting the corrected numbering as required.

With respect to the specification the examiner states the the application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). Applicant submits herewith an abstract of the disclosure on a separate sheet. Further, the Examiner indicates that lines 19-25 of page 8 of the specification are impossible to read due to the small font and poor quality of the copy. Applicants submit herewith a clean substitute page 8 of the specification.

Claims 1-7 were rejected under 35 U.S.C. § 101 because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility. Claims 1-7 were rejected under 35 U.S.C. § 112, first paragraph, because the claimed invention is not supported by either a clear asserted utility or a well established utility. Claims 1-3 also were rejected under 35 U.S.C. § 112, first paragraph, for containing subject matter which was not

disclosed in the specification in such a way as to enable one skilled in the art to which it pertains to make or use the invention. Finally, claims 2-6 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse these rejections for the following reasons.

Independent claim 1 as amended recites an isolated polynucleotide molecule encoding an effector protein for the Grb7 family of signalling proteins, wherein the polynucleotide molecule comprises a nucleotide sequence encoding an amino acid sequence as shown in SEQ ID NO:2. Dependent claims 5, 6 and 7 are directed to a host cell transformed with this polynucleotide molecule (claims 5 and 6) and a method of producing a protein by expressing the polynucleotide molecule.

In rejecting claims 1-7 under 35 U.S.C. § 101, it is the Examiner's position that the polynucleotide of the invention, isolated because of its similarity to a known DNA, and the encoded protein may reveal only through further characterization a specific and substantial credible utility. Therefore, the Examiner asserts the invention of the present application is incomplete and the invention has no "real world" utility. Applicants submit that the polynucleotide molecule of claim 1, as amended, and dependent claims 5, 6 and 7 has been substantially characterized and has specific and substantial credible utility to one skilled in the art as follows.

Before the priority date of the present application, the Grb7 family of SH2 domain containing proteins have been shown to be associated with oesophageal carcinoma (Tanaka et al.,

1997, Cancer Research 57: 28-31); primary gastric cancer (Kishi et al., 1997, Biochem. Biophys Res. Commun. 232(2): 5-9) and breast cancer (Stein et al., 1994, EMBO J. 13(6): 1331-40). Furthermore, the Grb7 family of proteins not only includes a motif which is characteristic of a protein involved in a signal pathway (an SH2 domain) but also a domain which is shared with a protein termed Mig10 which is involved in neuronal cell migration (Daly et al., 1996, J. BioI. Chem. 272: 12502-12510). SH2 domain-containing proteins are known to interact with tyrosine kinase receptors, which in turn are known to play a role in both cell cycle regulation and cell migration.

In addition, Grb7 has been shown to bind to Human EGF receptor 2, known to play an important role in a number of tumors including breast cancer (Stein et al., 1994). In the same report, Grb7 was shown to bind to tyrosine phosphorylated SHC. Subsequent reports have shown that Grb7 positively regulates cell migration (Tanaka et al., 1998, J. Clin. Invest. 102: 821-827; Han and Guan, 1999, J. BioI. Chem. 274: 24425-24430; and Tanaka et al., 2000, J. Clin. Invest. 183: 411-415) and this is likely to increase the invasion or metastasis of cancer cells.

These findings provide very strong evidence that the Grb7 family are signal transduction molecules the aberrant expression of which is associated with human tumors. The identification of cellular proteins which interact with SH2 domain proteins involved in cell signalling are important because these other cellular proteins are highly likely to be regulators or effectors of the function of the SH2 domain proteins. Consequently, the identification of a protein which binds to the Grb7 family of proteins, including Grb7 and Grb14, is an important finding.

The polynucleotide of the present invention has been identified using a yeast two hybrid screen on the basis of its binding to full length Grb14, a member of the Grb7 family (page 6 line 12 to page 9 line 23 of the specification). This immediately provides functional information about the newly identified polypeptide encoded by the polynucleotide of the invention i.e. the polypeptide has a proven biological function disclosed in the specification which is that it interacts with Grb14.

Furthermore, in the present application, the applicants have confirmed the binding properties of the newly identified protein using a GST pull down assay (page 10 line 26 to page 11 line 10), mapped the genomic position of the newly identified sequence (page 10 lines 11 to 24) and mapped the region of Grb14 to which the newly identified protein binds (page 11 lines 12 to 32). In addition, Northern blotting studies are described that demonstrate that the new sequence is expressed in all tissues except kidney cells (page 10 lines 4 to 10). This work represents a significant amount of real biochemical characterization.

The conclusions drawn in the specification from these data are that the protein encoded by clone 2.2412 represents a general effector of the Grb7 family (page 11 lines 9 and 10; page 11 lines 29 to 32). Given the characterisation of the Grb7 family already achieved by the priority date of the present application, the identification of a protein which binds to the Grb7 family of proteins would present the person skilled in the art with immediate and obvious utility. It is not necessary for the applicants to have established the precise function of the polypeptide disclosed in the present application to fulfil the utility requirements. The present application discloses a "real world" property of the polypeptide disclosed in the present application which is that the

polypeptide is expressed in the majority of human cells and binds to the Grb7 family of proteins which are already known to be implicated in tumor progression in humans.

The person skilled in the art would appreciate that this function alone renders the polypeptide disclosed in the present application of real use. Given the role of Grb7 in human cancers, it is a real and credible utility that the polypeptide disclosed in the present application can be used to affect Grb7 function, which would be expected to have therapeutic utility. It is not necessary for the applicants to have demonstrated actual therapeutic use. Applicants submit that the assessment made and conclusions drawn in the present specification from the available data and prior knowledge of the biological characteristics of the Grb-7 family would be considered reasonable and realistic by a person of ordinary skill in the art.

The applicants request that the Examiner should not be unduly influenced by the scientifically cautious use of the word "may" in the specification. Applicant submits that the specification discloses an asserted utility which would be considered by a skilled person to be credible given the knowledge in the art in relation to the Grb7 family of proteins, namely that the interaction between Grb7 and the polypeptide encoded by the nucleotide of the invention will provide a target for therapeutic intervention and/or that the levels of said polypeptide should provide a useful tumor marker/prognostic indicator for the same tumors in which Grb7 family members exhibit differential expression (page 5 lines 13 to 19).

The initial burden is on the Office to establish a prima facie case for a finding of lack of utility and provide sufficient evidentiary basis for that finding, and Applicants respectfully submit that the Examiner has not met this burden. As established by *In re Gaubert*, 524 F.2d

1222, 1224, 187 USPQ 664,666 (CCPA 1975), "the PTO must do more than merely question operability ..... it must set forth factual reasons that would lead one skilled in the art to question the objective truth of the statement of operability." The Office must establish that it is more likely than not that a person skilled in the art would not consider credible any specific and substantial utility asserted by the applicant for the claimed invention (MPEP 8th Ed. 2107 III.(A)).

Further, applicants submit that subsequent confirmation of the asserted utility overcomes the Examiner's rejections asserting a lack of utility. Specifically, applicant notes that the protein encoded by the claimed nucleotide sequence has subsequently been shown to be a novel human tankyrase, Tankyrase 2 (Lyons et al., 2001, J. BioI. Chem. 276: 17172-17180). Lyons et al. report the two hybrid work referred to in the present application, maps the binding sites on both partners, confirms the interaction in living cells by co-immunoprecipitation analysis and shows co-localisation to the low density microsome fraction. Importantly, two groups have confirmed the assertion made in the present application that Tankyrase 2 is a tumor marker. One group isolated Tankyrase 2 using sera from breast cancer patients (Kuimov et al., 2001, Genes and Immunity 2: 52-55) and the other group using sera from patients with meningioma (Monz et al., 2001, Clin. Cancer Res. 7: 113-119). These articles demonstrate that Tankyrase 2 is an antigen specific to a number of types of cancers.

Therefore, in view of the discussion above, the present invention of a polynucleotide molecule encoding an effector protein for the Grb7 family of signalling proteins as disclosed in the present application is operable and has specific and substantial credible utility. As a result, the polynucleotide molecule of the current invention as set forth in claim 1, as amended, which

incorporates the limitation that the polynucleotide molecule comprises a nucleotide sequence encoding an amino acid sequence as shown in SEQ ID NO:2, has specific and substantial credible utility. Claims 5, as amended, 6, as amended and 7, as amended, depend from claim 1, either directly or through their dependence from a claim which is dependent from claim 1, and are patentable by virtue of their dependence. With respect to claims 2-4, these claims are cancelled and the rejection with respect to these claims is, therefore, rendered moot.

The Examiner in rejecting claims 1-7 under 35 U.S.C. § 112, first paragraph, asserts that one skilled in the art would not know how to use the claimed invention because it is not supported by either a clear asserted utility or a well established utility. Applicants submit that the application does teach one skilled in the art how to use the invention as discussed above. Further, Applicants submit that the invention as claimed is supported by a well established utility as discussed above. Therefore, the specification clearly does set out to one skilled in the art how to use the invention of the amended claims 1, 5 and 6 and claim 7. With respect to claims 2-4, these claims are cancelled and the rejection with respect to these claims is, therefore, rendered moot.

In rejecting claims 1-3 under 35 U.S.C. § 112, first paragraph, the Examiner states that claims 1-3 contain subject matter which was not described in the specification in such a way as to enable one skilled in the art ot make and/or use the invention, where these claims are directed to polynucleotides which have 75%, 85% and 95% sequence identity to the polynucleotide as shown in SEQ ID NO:1. Claim 1, as amended, is directed to a polynucleotide molecule comprising a nucleotide sequence encoding an amino acid sequence as shown in SEQ ID NO:2. These polynucleotide molecules are described in the specification, which discloses the amino

acid sequence which is encoded. Thus, there is sufficient written description to inform a skilled artisan that the applicatants were in possesion of the claimed invention at the time the application was filed. Therefore, the subject matter of claim 1, as amended, is adequately described in the specification in such a way as to enable one skilled in the art to make/or use the invention. With respect to claims 2 and 3, these claims are cancelled and the rejection with respect to these claims is, therefore, rendered moot.

Claims 2-6 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as their invention. It is the Examiner's position that there is insufficient antecedent basis for the limitation "a polynucleotide molecule" in claims 2-5. Claim 5, as amended, is directed to a host cell transformed with the polynucleotide molecule of claim 1 and more clearly defines the subject matter of the invention. With respect to claims 2-4, these claims are cancelled and the rejection with respect to these claims is, therefore, rendered moot. The Examiner also rejected claim 4 on the basis that the terms "which subtantially corresponds to" renders the claim indefinite. Claim 4 is cancelled and the rejection with respect to this claim is, therefore, rendered moot. Finally, it is the Examiner's position that there is insufficient antecedent basis for the limitation "a host cell" in claim 6. Claim 6, as amended, is directed to the host cell of claim 5 and more clearly defines the subject matter of the invention. Therefore, claims 5 and 6, as amended, more clearly define and distinctly claim the subject matter which applicant regards as the invention.

Applicants submit that the present application is now in condition for allowance. Reconsideration and favorable action are earnestly requested.

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1871-129.AM3

Amended Specification with marked-up versions:

Page 6, third full paragraph:

[**Figure 1** provides] **Figures 1A-1C** provide the nucleotide and amino acid (single letter code) sequence of 2.2412. Numbers refer to distances in base pairs. Ankyrin-type repeat sequences are underlined. An additional repeat squence is indicated by italics. Ths stop codon is represented by an asterisk. The original cDNA clone 2.2412 isolated by the two hybrid screen spans nucleotides 694-2664 of this sequence.

Page 9, second and third full paragraphs:

A novel cDNA of 1971 bp. designated 2.2412. was also isolated. This clone encoded a polypeptide of 657 amino acids in frame with the Ga14 DNA-BD. The cDNA did not contain a stop codon. and this. together with the Northern analysis described below. indicated that it was incomplete. This DNA fragment was therefore used as a probe to screen a human placental cDNA library (5' STRETCH PLUS. Clontech. in λgt10). This resulted in the isolation of two clones. designated clone 8 and clone 12. Clone 8 was approximately 2 kb and overlapped the original 2.2412 clone by 900 bp at the 3' end. This clone provided the carboxy-terminal end of the 2.2412 protein sequence [(Figure 1)] (Figures 1A-1C). Clone 12 was approximately 3.5 kb and to date has provided an additional 692 bp of sequence information in the 5' direction. The nucleotide and protein sequence for 2.2412 provided by these overlapping clones is shown in

[Figure 1] Figures 1A-1C. Since a 5' initiation condon has yet to be identified the coding sequence still appears to be incomplete.

Database searches using the 2.2412 cDNA sequence revealed significant homology with a large number of proteins containing ankyrin-like repeats. These sequences were first identified as homologous regions between certain cell cycle regulatory proteins and the Drosophila protein Notch (Breeden and Nasmyth. Nature 329. 651-654. 1987) but subsequently they have been identified in a wide variety of other proteins where they are thought to function in protein-protein interactions (Bork. Proteins 17. 363-374 1993). Subsequent analysis of the protein sequence identified 18 consecutive ankyrin repeats and an additional repetitive element [(Figure 1)] (Figures 1A-1C). The ankyrin repeat region is followed by a stretch of approximately 40 amino acids rich in serine residues. The remaining C-terminal region has a relatively high content of charged amino acids.

Page 10, third full paragraph:

cDNAs encoding the full length and – and C-terminal regions of the original 2.2412 cDNA clone (nucleotides 694-2664, 694-1614 and 16152664 of the sequ3nce shown in [Figure 1] Figures 1A-1C, respectively) were cloned into the vector pGEX4T2 (Pharmacia). The full length construct was generated by subcloning from the pACT2 clone as a Ndel fragment, whereas the shorter constructs were synthesized by directional cloning of PCR products. The corresponding GST-fusion proteins were purified from IPTG-induced bacterial cultures using glutathione-agarose beads (Smith and Johnson, Gene 67, 31-40, 1988). These immobilized fusion proteins were then incubated with lysates from cells expressing Flag epitope-tagged Grb14

[Daly *et al.* 1996 *supra*) or human breast cancer cells expressing high levels of Grb7 (SK-BR-3: Stein et al. 1994) as described previously (Daly et al. 1996). Following washing, bound proteins were detected by Western blot analysis. The results indicated that 2.2412 bound specifically to both Grb14 and Grb7 *in vitro*, and that the N-terminal fusion protein bound more strongly than that derived rom the C-terminus. These data, obtained using a different methodology for detecting protein-protein interactions to the yeast two hybrid system. confirm that 2.2412 interacts with Grb14. Furthermore, 2.2412 also binds Grb7. Consequently 2.2412 appears to represent a general effector for the Grb7 family.

Amended Claims 1, 5 and 6: Version with markings to show changes made

1. (Amended) An isolated polynucleotide molecule encoding an [a candidate] effector protein for the Grb7 family of signalling proteins, wherein the polynucleotide molecule comprises a nucleotide sequence encoding an amino acid sequence [having at least 75% sequence identity to that] as shown [as] in SEQ ID NO:[1] 2.

5. (Twice amended) A host cell transformed with [a] the polynucleotide molecule [according to] of claim 1.

6. (Amended) [A] The host cell [according to] of claim 5, wherein the host cell is a mammalian, insect, yeast or bacterial host cell.